Stimulus methods for recording pain-related SEF

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1. Introduction

The cerebral representation of pain perception in humans is poorly understood compared with that of other sensations such as touch or vibration. This is mainly because of a lack of appropriate instrumentation for stimulation and recording [1]. To our knowledge, only a few systematic studies of somatosensory evoked magnetic field (SEF) following painful stimulation (pain-related SEF) have been conducted. Hari et al. [2] used painful electrical stimulation of tooth pulp. Huttunen et al. [3] and Hari et al. [4] used CO_2 gas stimulation of the nasal mucosa. Howland et al. [5] applied high-intensity painful electrical stimulation and reported that the equivalent current dipoles (ECD) were located at or near the second somatosensory cortex (SII) or the frontal operculum. We used the same method and found ECD in not only the SII but also the cingulate cortex [6-8]. A low power and long wavelength CO_2 laser beam induces sensations of pain or heat when applied to the skin. We have, therefore, recorded pain-related SEF following painful CO_2 laser stimulation to elucidate the mechanisms of pain processing in the human brain [9-12]. Bromm et al. [13] also reported SEF following painful CO_2 laser stimulation. We recently developed a new device which induced painful impact stimuli [14]. An airgun was placed outside a shielded room and small plastic bullets were fired at the arm and trunk at different intensities. The evoked pain-related SEF responses had a major component with characteristic polarity-reversal deflections, and the ECD were estimated in the SII of the bilateral hemispheres.

In this paper, we describe two major methods for recording pain-related SEF, high-intensity painful electrical stimulation and painful CO_2 laser stimulation.

2. Pain-related SEF following painful electrical stimulation

Pain-related SEF produced by high-intensity painful electrical stimulation of the skin showed predominant middle-latency potentials, 1M and 2M, the peak latencies of which were approximately 90 and 160 msec, respectively. Similarly, 2 components, N150 and P220, of pain-related somatosensory evoked potential (pain-related SEP) were also recorded in response to the painful electrical stimulation [6-8,15,16]. Neither pain-related SEF nor SEP components are identified when the stimulation is painless. Therefore, these particular components were considered to be generated by specific pain-related brain activities. However, peak latencies of SEP (N150 and P220) were clearly longer than those of SEF (1M and 2M) [8,16]. In addition, the SEP components were significantly affected by attention (or distraction) [8] or by a famous method of pain relief, taranscutaneous electrical nerve stimulation (TENS), [16], but SEF components were not. Therefore, we consider that the SEF components reflect the primary activities and the SEP components the secondary activities involving cognitive functions.

We usually adopt a stimulus intensity which causes a definite painful sensation, depending on the subject’s subjective feeling and stimulus sites, ranging from approximately 8 to 30 mA (mean 15 mA) with a stimulus duration of 1 msec. A pulse train of stimulus, for example a 5-pulse train (0.2 msec pulse duration, 100Hz frequency) [6] or 25-pulse train (0.5 msec pulse duration, 500 Hz frequency) [17], is also used. In this case, the lower stimulus intensity, 5-15 mA, may be enough. A random stimulus rate, 0.3-0.8 Hz, is more appropriate. The amplifier frequency response is 0.1 – 50 or 100 Hz, and the analysis time is 100 msec before and 500 msec after the stimulation. Fifty to 100 responses are averaged in one recording, and at least 2 recordings are done to confirm the reproducibility. Various other stimulus methods, for example, intracutaneous stimulation of the finger tip, have been reported [5]. A subjective pain rating scale (0-10 scales) such as the visual analogue scale (VAS) is useful to know the subjective feeling of subjects.

The biggest advantage of pain-related SEP as well as SEF following electrical stimulation is that the method is very simple and easy. However, a problem with this method is that not only pain-related small myelinated fibers but also the large myelinated fibers (Aα fibers and/or Aβ fibers), relating to tactile, vibration or proprioception sensations, are activated. In other words, these components are not the "pure" pain-related ones.

Generator sources for each recognizable SEF component were analyzed [5-8,16]. When we applied 5-train pulses to the right index finger, short-latency components within approximately 80 msec of the stimulation were generated in the hand area of the primary somatosensory cortex (SI). The first pain-specific component, 1M, was generated in the SII or insula of the bilateral hemispheres, and the second one, 2M, was generated in the bilateral SII-insura and the cingulate cortex [6-8]. These results indicate that the SII-insula areas in the bilateral hemispheres are first activated by the painful stimulation and then the signals relating to pain perception spread to the cingulate cortex.

The clinical application of pain SEP and SEF is not widespread [17], probably because of a lack of basic knowledge including about the generator sources. However, this method is simple as compared with laser stimulation, and we think it should be used more often for the clinical diagnosis of pain-specific physiological problems.

3. Pain-related SEF following painful CO_2 laser stimulation

CO_2 laser stimulation (10.6 μm wavelength) has become popular for the following reasons; (1) pure noxious stimulation without excitation of mechanoreceptors of the skin, (2) no temporal delay between the stimulus time and the onset of averaging, (3) high synchronization of neural receptor activation, (4) a wide range of adjustable stimulus parameters,, (5) nearly complete absorption, (6) low penetration of the heat-sensitive nerve terminals and (7) invisibility to the human eye. The biggest disadvantage of CO_2 laser stimulation is that it burns (erythema) the superficial skin with high intensity, though the burn heals completely. Unfortunately, a laser stimulator for recording pain-related SEP and SEF is not on the market at present except for one thulium laser stimulator sold in Germany. Therefore, researchers must order a custom-made stimulator or alter other devices such as a laser knife for surgery by themselves to achieve this particular objective.

Laser beam stimulation is 2 to 10 mm in diameter, and 10 to 50 msec in duration. It is applied with a 3 to 10 msec random interstimulus interval, and rotation of the stimulation spot to avoid sensitization and burn is necessary. Stimulus strength must be changed depending on the above factors. In addition to the strong pain which is enough to record clear components, a slight pain to measure the pain threshold is also necessary. The amplifier frequency response is 0.1 – 30 or 50 Hz. From 25 to 50 trials are averaged, but the number averaged actually depends on the quality of the waveforms. Only 10-20 trials is enough in some recordings. Analysis time is usually 100 msec before and 1 sec after the stimuli, but 3 sec is adopted when we record the ultra-late components reflecting signals ascending through C fibers. A subjective pain rating scale, VAS, is useful to know the subjective feeling of subjects.

Following upper limb stimulation, a consistent and clear magnetic field (termed 1M) was identified in the bilateral cerebral hemispheres. Its onset and peak latencies varied among the subjects, being about 120-180 and 180-220 msec, respectively. Peak latencies of two major components of pain-related SEP, whose peak latencies were about 240 and 340 msec, were clearly longer than those of 1M of SEF [9,10,12]. When a conventional single ECD analysis was used, the ECD was estimated to be located around the SII or insula in bilateral hemispheres [9-12]. The peak latency of the SII response recorded from the hemisphere contralateral to the stimulation was significantly ($P<0.01$) shorter (approximately 20-25 msec) than that recorded from the ipsilateral hemisphere [12].

Since various sites are thought to be responsible for pain perception, we adopted a multi-dipole model, brain electric source analysis (BESA), for elucidating mechanisms of pain perception in humans [11]. The residual variance (%RV) indicated the percentage of data which cannot be explained by the model. The goodness of fit (GOF) was expressed in % as

(100 - %RV). The results showed that the 4-dipole model was the most appropriate. Source 1 and 2 was located in the SII in the hemisphere contralateral and ipsilateral to the stimulation, respectively, and source 3 and 4 in the anterior medial temporal area, around the amygdalar nuclei or hyppocampal formation, in the hemisphere contralateral and ipsilateral to the stimulation, respectively. The GOF of this model was over 90%.

Recently, Posner et al. [18,19] and Kanda et al. [20] reported the activities in SI in response to laser stimulation. Interestingly, three spatially segregated cortical areas (contralateral SI and bilateral SII) were simultaneously activated at around 210 msec after the stimulus, suggesting parallel processing of pain information in SI and SII. Both Posner et al. [19] and Kanda et al. [20] speculated that area 1 of SI is the generator source. This interesting and important point should be clarified in the future studies.

Pain perception was changed by attention or distraction effects. Therefore, we aimed to compare the effects of distraction on pain-related SEF and SEP [12]. Painful CO_2 laser stimuli were applied to the right forearm of ten healthy subjects. A table with 25 random two-digit numbers was shown to the subjects, who were asked to add 5 numbers of each line in their mind (calculation task) or to memorize the numbers (memorization task) during the recording. Subjects declared VAS for rating subjective pain during each condition. The distraction tasks did not affect the SEF components, but significantly attenuated SEP components. The change of VAS score showed a positive correlation with a change of amplitude of SEP components, but not SEF components. Like pain-related SEP and SEF following painful electrical stimulation [8,16], the differences of latency and distraction effects between SEP and SEF probably reflect different brain activities. We suspect that the 1M of SEF generated in SII-insula reflects the initial cortical activation in response to painful stimulation. The SEP components are considered to represent the activities of multiple areas including the SII-insula and the limbic system, and it seems reasonable that the activities in those areas are affected by attentional changes.

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